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EXAMINER	
REDDIG, PETER J	
ART UNIT	**PAPER NUMBER**
1642	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/531,415	BERDEL ET AL.	
	Examiner	Art Unit	
	Peter J. Reddig	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 October 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37-39,41-53,61-64 and 73-76* is/are pending in the application.

4a) Of the above claim(s) *61-64 and 73-76* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37-39,41-53 and 77* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The Amendment filed October 15, 2009 in response to the Office Action of April 16, 2009 is acknowledged and has been entered. Previously pending claims 58-60 have been cancelled and claims 37-39, 41-53, and 77 have been amended. Claims 61-64 and 73-76 have been previously withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions. Claims 37-39, 41-53, and 77 are currently being examined.

Rejections Maintained
Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 42 and 43 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the reason set forth in the Office Action of April 16, 2009, section 4, which are set forth below.

Claims 42 and 43 are drawn to the compound of claim 37 wherein the first binding domain has a binding affinity of 10^{-5} to 10^{-12} or a binding affinity of 10^{-7} to 10^{-9}. However, the claims have no limitation as to the units of the claimed binding affinities or to what binding the binding affinities refer. Thus, in the absence of units for the affinity or what binding interaction refers to, it can not be determined what the scope of the binding affinity is.

Section 2171 of the M.P.E.P. states

> *There are two separate requirements set forth in this paragraph:*
> *(A) the claims must set forth the subject matter that applicants regard as their invention; and*
> *(B) the claims must particularly point out and distinctly define the metes and bounds of the subject matter that will be protected by the patent grant.*
>
> *The first requirement is a subjective one because it is dependent on what the applicants for a patent regard as their invention. The second requirement is an objective one because it is not dependent on the views of applicant or any particular individual, but*

> *is evaluated in the context of whether the claim is definite — i.e., whether the scope of the claim is clear to a hypothetical person possessing the ordinary level of skill in the pertinent art.*

In the instant case of the claimed binding affinities, one of skill in the art could find representative examples in the art which have been defined in such terms, however, it is unclear at what point one of skill in the art would be infringing on the claims without limitations as to the metes and bounds of the binding affinities and the amount of deviation acceptable.

Applicants' argue that claims 42 and 43 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. The Examiner stated that "in the absence of units for the affinity or what binding interaction refers to, it can not be determined what the scope of the binding affinity is." Office Action at page 5. Applicants respectfully disagree with the Examiner's rejection. Applicants respectfully submit that one of ordinary skill in the art would recognize that the binding affinities recited in present claims 42 and 43 refer to the affinity of the first binding domain for the tumor-specific molecule. In order to clarify what binding interaction refers to, Applicants have amended claims 42 and 43 to recite that the binding affinity of the first binding domain is for the tumor-specific molecule. Furthermore, Applicants respectfully submit that a person of ordinary skill in the art would recognize that binding affinities are expressed in terms of a dissociation constant, and that dissociation constants are well-known by those in the art to have molar (M) units. See, e.g., Alberts, et al. (2008). Molecular Biology of the Cell. New York, NY: Garland Science, Taylor & Francis Group, LLC. Therefore, Applicants respectfully submit that "a binding affinity of 10^{-5} to 10^{-12}" means that the dissociation constant of the first binding domain and the tumor-specific molecule is 10^{-5} M to 10^{-12} M. Therefore, Applicants respectfully submit that claims 42 and 43 are definite, and submit that the Examiner's rejection of these claims under 35 U.S.C. § 112, second paragraph, has been overcome and should be withdrawn

Applicants' arguments have been considered, but have not been found persuasive because whether or not binding affinity is generally defined in molar units; neither the specification nor the claims define or limit the binding affinity to such units. Thus, given the claims remain unlimited by units for the binding affinity one of skill in the art would not know at what point one would be infringing on the claims without limitations as to the metes and bounds of the binding affinities and the amount of deviation acceptable.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 37- 39, 41-51, and 77 remain rejected as failing to comply with the written description requirement for the reasons set forth in section 7 of Office Action of April 16, 2009, which are set forth below.

The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn to a compound comprising a first binding domain for a tumor-specific molecule and a second binding domain to effect dyslocalization, wherein said compound is a peptide, oligoprotein, protein, or fusion protein and is able to effect dyslocalization of the tumor- specific molecule or a compound comprising a binding domain for a tumor-specific molecule and a DNA-binding domain, wherein said compound is a peptide, oligoprotein, protein, or fusion protein and is able to effect dyslocalization of the tumor- specific molecule. The claims lack any limitation on said compounds and thus are drawn to a genus of compounds comprising a first binding domain for a tumor-specific molecule and a second binding domain to effect dyslocalization, wherein said compound is a peptide, oligoprotein, protein, or fusion protein and is able to effect dyslocalization of the tumor- specific molecule or compounds comprising a binding domain for a tumor-specific molecule and a DNA-binding domain, wherein said compound is a peptide, oligoprotein, protein, or fusion protein and is able to effect dyslocalization of the tumor- specific molecule. When given the broadest reasonable interpretation, the terms compound comprising a first binding domain for a tumor-specific molecule and a second binding domain to effect dyslocalization, wherein said compound is a

peptide, oligoprotein, protein, or fusion protein and is able to effect dyslocalization of the tumor-specific molecule or a compound comprising a binding domain for a tumor-specific molecule and a DNA-binding domain, wherein said compound is a peptide, oligoprotein, protein, or fusion protein and is able to effect dyslocalization of the tumor- specific molecule encompasses a wide genus of compounds that is highly variant which vary significantly both in structure and function from each other. The description of GFP-M&M/SEQ ID NO: 1 as a compound comprising a first binding domain for a tumor-specific molecule and a second binding domain to effect dyslocalization, wherein said compound is a peptide, oligoprotein, protein, or fusion protein and is able to effect dyslocalization of the tumor- specific molecule or a compound comprising a binding domain for a tumor-specific molecule and a DNA-binding domain, wherein said compound is a peptide, oligoprotein, protein, or fusion protein and is able to effect dyslocalization of the tumor- specific molecule fails to adequately describe the genus of compounds because said genus tolerates members which differ significantly in both structure and function from GFP-M&M/SEQ ID NO: 1. One of skill in the art can reasonably conclude that applicant was not in possession of a genus of a compound comprising a first binding domain for a tumor-specific molecule and a second binding domain to effect dyslocalization, wherein said compound is a peptide, oligoprotein, protein, or fusion protein and is able to effect dyslocalization of the tumor- specific molecule or a compound comprising a binding domain for a tumor-specific molecule and a DNA-binding domain, wherein said compound is a peptide, oligoprotein, protein, or fusion protein and is able to effect dyslocalization of the tumor- specific molecule at the time the invention was filed.

Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

It is noted that as of the filing date a few compounds like the claimed compounds were known in the art (for example, Steffen et al. (Proc. Natl. Acad. Sci. USA July 8, 2003, 100: 8448-8453, IDS) and WO 01/73433 A2 (Minucci et al. October 4, 2001)), however, these few

compounds fails to adequately describe an entire genus because the genus is highly variant encompassing members which differ significantly in structure from the art known compounds.

In the instant case the genus is only described as a definition by function (i.e. binding and delocalizing a tumor specific molecule), and beyond that of a few examples of such compounds in the art, one of skill in the art cannot readily visualize or recognize the identity of members of the genus in the absence of knowledge as to what that material consists of.

Applicants argue that the dyslocalization of AML 1-ETO effected by GFP-M&M was disclosed in the present application and Applicants were in possession of the claimed invention as a whole at the time of filing of the present application. In light of the specification, the general concept of selecting and combining a tumor-specific molecule and a dyslocalization-effecting molecule is disclosed. Determination of what is needed to support generic claims to biological subject matter depends on a variety of factors, such as the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, the predictability of the aspect at issue, and other considerations appropriate to the subject matter. See Capon v. Eshhar, 418 F.3d 1349, 76 U.S.P.Q.2d 1078. In light of the present application, a person skilled in the art could make a compound comprising a first binding domain for a tumor-specific molecule and a second domain to effect dyslocalization. A person skilled in the art would recognize that the methods and compounds of the present invention could be readily adapted to utilize first and second binding domains that differ from GFP-M&M and would have a reasonable expectation of success. Applicants submit that at least sequences would be known by a person in light of the specification. Therefore, as structures and functions of the binding domains are described by the present specification, the sequences can be determined by one skilled in the art as they are largely known. As in Capon, Applicants are disclosing a chimera, wherein the structure an function of the two parts of the chimera (a first binding domain for a

tumor-specific molecule selected from the group consisting of AML1-ETO, BCR-Abl, PML-RARalpha, PLZF- RARalpha, MLL or EWS-FLI fusion protein and a second binding domain to effect dyslocalization of said tumor-specific molecule) are known.

Applicants argue that a person skilled in the art would be able to make and use the claimed compound utilizing first and second binding domains that differ from GFP- M&M. As such, Applicants were in possession of the presently claimed invention. Applicants therefore respectfully submit that the Examiner's rejection of claims 37-51 and 77 under 35 U.S.C. § 112, first paragraph has been overcome and should be withdrawn.

Applicants' arguments have been considered, but have not been found persuasive because the claims encompass a large genus of compounds with a first binding domain and second binding domain, which encompasses a genus of compounds inclusive of protein and non-protein molecules, such as nucleic acids or small chemical molecules. See p. 6-lines 10-25 of the specification. Thus, the description of GFP- M&M or other proteins binding to AML1-ETO, BCR-Abl, PML-RARalpha, PLZF- RARalpha, MLL or EWS-FLI in the art is not sufficient to describe the genus to effect dyslocalization of these compounds because the genus is highly variant and neither the specification nor the art has described the structure function relationship between this large genus of compounds and binding to the claimed tumor specific molecules. Additionally, DiMartino and Cleary (Br. J. Haematology 1999, 106: 614-626) teach that MLL rearrangements encompass a diverse groups of chromosomal rearrangements involving the of the MLL gene on chromosome 11q23. See p. 614 Tables I and II. Additionally, DiMartino and Cleary teach that identifying the final common pathway involved in MLL fusion protein and transformation remains an ultimate goal of the field and will required continued structure

function studies to define the portions of the protein required for transformation and identification of interacting partners. See p. 623-1st col. Thus, the structure and function of the broadly claimed MLL in transformation processes like cell growth and apoptosis has not been defined. Thus, in absence of a description of the structure and function of the MLL proteins encompassed by the claims, the specification has not provided an adequate written description of the claimed compounds for binding to it for its dyslocalization.

New Grounds of Rejection

Claim Objections

4. Claim 41 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 41 is drawn to a tumor specific molecule that is a peptide, oliogopeptide, protein, or fusion protein, which is broader in scope than the tumor specific molecule of claim 37, which is selected from the group consisting of AML1-ETO, BCR-Abl, PML-RARalpha, PLZF-RARalpha, MLL, and EWS-FLI.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 37-39, 41-45, 47-53 and 77 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "MLL" in claims 39, 41-45, 47-53 and 77 is a relative term which renders the claims indefinite. The term "MLL" is not defined by the claim, the specification does not define what MLL, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. DiMartino and Cleary (Br. J. Haematology 1999, 106: 614-626) teach that MLL rearrangements encompass a diverse groups of chromosomal rearrangements involving the of the MLL gene on chromosome 11q23. See p. 614 Tables I and II. However, neither the specification, nor the claims teach what MLL is intended to encompass, one of the rearranged genes or the wild type MLL, thus rendering the scope of the claims indefinite.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 37-39, 41-45, 47-53, and 77 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a purified compound comprising a first binding domain for a tumor-specific molecule selected from the group consisting of AML 1-ETO, BCR-Abl, PML- RARalpha, PLZF-RARalpha, and EWS-FLI fusion protein and a second binding domain, wherein said compound is a peptide, oligoprotein, protein, or fusion protein, to effect dyslocalization of said tumor-specific molecule, wherein said dyslocalization is to a site where said tumor- specific molecule is not normally present in tumor cells, *does not* reasonably provide enablement for a purified compound comprising a first binding domain for a tumor-specific molecule selected from the group consisting of AML 1-ETO, BCR-Abl, PML-RARalpha, PLZF-RARalpha, **MLL** and EWS-FLI fusion protein and a second binding domain to effect dyslocalization of said tumor-specific molecule, wherein said dyslocalization is to a site

where said tumor- specific molecule is not normally present in tumor cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims are broadly drawn to a purified compound comprising a first binding domain for a tumor-specific molecule selected from the group consisting of AML 1-ETO, BCR-Abl, PML- RARalpha, PLZF-RARalpha, **MLL** and EWS-FLI fusion protein and a second binding domain to effect dyslocalization of said tumor-specific molecule, wherein said dyslocalization is to a site where said tumor- specific molecule is not normally present in tumor cells. Additionally the dyslocalization encompasses inhibiting the growth of tumor cells or inducing apoptosis of tumor cells expressing the tumor specific molecule or wherein the dyslocalization binds the tumor-specific molecule to a nucleic acid sequence which regulates the transcription of a gene, thereby activating or inhibiting the transcription of the gene.

The specification teaches that a recombinant fusion protein was constructed from the AML1 binding domain of the myeloid like ELF factor (MEF), the DNA binding domain of c-myb and the green fluorescent protein (GFP) and was called GFP-M&M, see p. 20-21. The specification teaches that GFP-M&M binds to MYB DNA binding sites, binds AML1-ETO to c-kit promoter elements, inhibits myb dependent promoter activity in the presence of AML1-ETO, inhibits colony formation of the hematopoietic 32D cell line expressing AML1-ETO, induces apoptosis in the AML1-ETO hematopoietic 32D cells, and did not repress MYB dependent promoters in the absence of AML1-ETO, See pages 21-25 and the figures. The specification teaches that MLL fusion proteins are one of the tumor specific molecules to be attacked.

One of skill in the art cannot predictably extrapolate the teachings of the specification to the enablement of the claims because MLL encompasses a wide range of proteins for which binding domains have not been determined and the effect of dyslocalization MLL on cell growth and apoptosis has not been determined. DiMartino and Cleary (Br. J. Haematology 1999, 106: 614-626) teach that the MLL rearrangements encompass a diverse groups of chromosomal rearrangements involving the of the MLL gene on chromosome 11q23. See p. 614 Tables I and II. DiMartino and Cleary teach that the MLL rearrangements can occur in the absence of leukemia. See p. 617- 2nd col. DiMartino and Cleary teach that the ability of MLL fusion protein to transform hematopoietic cells may depend on the on the transcriptional program active in the cell. See p. 619, 2nd col. DiMartino and Cleary teach that identifying the final common pathway involved in MLL fusion protein and transformation remains an ultimate goal of the field and will required continued structure function studies to define the portions of the protein required for transformation and identification of interacting partners. See p. 623-1st col. Thus, the structure

and function of the broadly claimed MLL in transformation has not been defined and MLL proteins encompassed by the claims include the wild type and fusion proteins that are not involved in tumor cell growth or apoptosis. Given the above one of skill in the art would not predictably be able to make and use the invention as broadly claimed for dyslocalization of MLL proteins and inhibition of tumor cell growth, induction of apoptosis, or the alteration of gene transcription because predicting protein function from structure in protein biochemistry is not predictable and undue experimentation would be required to make and use the invention as broadly claimed. In particular, Bowie et al (Science, 1990, 247:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex (col. 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col. 2, p. 1306). These observations have been further supported by the findings of Skolnick et al. (TIBTECH 18:34-39, 2000), stating: "Knowing a protein's structure does not necessarily tell you its function" (Box 2, p. 36), noting that "alternatives are needed to assign the biochemical function of the 30-50% of proteins whose function cannot be assigned by any current methods"

(second column, p. 37). Additionally, Ibragimova and Eade (Biophysical Journal, Oct 1999, Vol. 77, pp. 2191-2198) teach that factors affecting protein folding and stability are governed by many small and often opposing effects and that even when the "rules" are know for altering the stability of a protein fold by the introduction of a single point mutation the result is not reliable because the balance of forces governing folding differs for different protein sequences, and that the determination of the relative magnitude of the forces governing the folding and stability of a given protein sequence is not straightforward (page 2191, first column, lines 12-17 and second column, lines 3-8). Further, Scott et al. (Nature Genetics, 1999, 21:440-443) teach that the gene causing Pendred syndrome encodes a putative transmembrane protein designated pendrin. Based on sequence similarity data, the authors postulated that the putative protein was deemed to be a member of sulfate transport protein family since the putative protein had a 29% identity to rat sulfate-anion transporter, 32% similarity to human diastrophic dysplasia sulfate transporter and 45% similarity to the human sulfate transporter. However, upon analyzing the expression and kinetics of the protein, the data revealed no evidence of sulfate transport activity wherein results revealed that pendrin functioned as a transporter of chloride and iodide. Scott et al suggest that these results underscore the importance of confirming the function of newly identified gene products even when database searched reveal significant homology to proteins of known function (page 411, 1st column, 4th paragraph). Additionally, Pero et al. (US PG Pub 2003/0105000, 2003) specifically teach that the SH2 domain of Grb14 is 81% similar to the SH2 domain of Grb7 on the amino acid level, but although Grb7 binds to ErbB2, Grb14 does not bind to ErbB2. Further, although the SH2 domain of Grb2 is only 50 % similarity to Grb 7 on the amino acid level, both Grb2 and Grb7 bind to the same site on ErbB2, see para 0255 of the

published application. Thus, sequence identity or similarity alone cannot be used to predict the function of a protein and extrapolating protein function from structure is unpredictable in protein biochemistry.

Given the breadth and unknown function of the MLL proteins claims, given the lack of a predictable structure function correlation in the art, one of skill in the are could not predictably make and use the contemplated compounds for dyslocalization of MLL proteins and inhibition of tumor cell growth, induction of apoptosis, or the alteration of gene transcription without undue experimentation. Additionally, it is noted that the specific compounds of claim 52 and 53, which are compounds that effect dyslocalization of AML-1 ETO, would not be expected to bind to and delocalize all of the claimed tumor specific molecules as these molecules do not contain binding domains for all of the tumor specific molecules claimed. The specification provides insufficient guidance with regard to these issues and provides insufficient working examples which would provide guidance to one skilled in the art and insufficient evidence has been provided which would allow one of skill in the art to predict that the invention will function as claimed with a reasonable expectation of success. For the above reasons, undue experimentation would be required to practice to make and use invention as broadly claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 37-39, 41-45, and 47 remain or are rejected under 35 U.S.C. 102(b) as being anticipated by McWhirter et al. (Mol. and Cell. Biol. 1993, 13: 7587-759, previously cited) as evidenced by Wu et al. (Oncogene 1999, 18: 4416-4424).

It is noted that given the indefinite nature of claims 42 and 43, given their broadest reasonable interpretation, claims 42 and 43 are drawn to the first binding domain having any binding affinity to any other molecule.

McWhirter et al. teaches isolated BCR which has a coiled-coiled domain that facilitates interaction with BCR-Abl and other protein interaction or binding domains, like a SH2 domain and a Rac-GAP domain. See Abstract, p.7591-1st col. and Fig. 1- 6.

Wu et al. teach that BCR negatively regulates BCR-ABL and reduces its transforming potential and caused cell death in BCR-Abl expressing cells. See Abstract, p. 4418 and Fig. 3.

Given that BCR can interact with BCR-Abl through the coiled coil domain and second binding domains for binding distinct proteins, BCR would be a purified compound comprising a first binding domain, the coiled coil domain, for BCR-Abl and a second binding, SH2 or RacGAP, to effect dyslocalization of BCR-ABL.

Although the reference does not specifically state that BCR delocalizes BCR-ABL to a site not that they are not normally present in tumor cells, induce apoptosis of a tumor cell expressing said BCR-Abl, given that proteins comprise the claimed domains, given that Wu et al. teach that BCR negatively regulates BCR-ABL and reduces its transforming potential and caused cell death in BCR-Abl expressing cells, the claimed product appears to be the same as the prior art product, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the

prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed method is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977).

Applicants argue that the Examiner stated that "McWhirter et al. teach that the BCR sequences of BCR-Abl proteins alter the sub-cellular localization of the Abl protein by blocking its nuclear translocation and activating the F-actin binding functions." Office Action at page 22. McWhirter does not describe a purified compound comprising a first binding domain for a tumor-specific molecule selected from the group consisting of AML 1-ETO, BCR-Abl, PML-RARalpha, PLZF-RARalpha, MLL and EWS-FLI fusion protein and a second binding domain to effect dyslocalization of the tumor-specific molecule, where the dyslocalization is to a site where the tumor-specific molecule is not normally present in tumor cells.

Applicants argue that BCR-Abl is defined in the present specification as tumor-specific molecule. See specification as filed at page 7, line 3. Abl is a domain within the BCR-Abl protein and is not itself a tumor-specific molecule, contrary to the Examiner's assertion. A person skilled in the art would recognize that Abl is a ubiquitously expressed tyrosine kinase that has been implicated in processes of cell differentiation, cell division, cell adhesion and stress response. While the BCR domain of the BCR-Abl molecule may be responsible for altering the subcellular localization of the Abl domain of the BCR-Abl molecule, Applicants submit that BCR does not effect dyslocalization of a tumor specific molecule, because Abl is not a tumor specific molecule.

Applicants argue that furthermore, the tumor-specific molecule is selected from the group consisting of AML1-ETO, BCR-Abl, PML-RARalpha, PLZF-RARalpha, MLL and EWS-FLI fusion protein.

Applicants argue that as McWhirter does not expressly disclose every element of the present claims either alone or as evidenced by Muller, Applicants respectfully submit that the Examiner's rejection of claims 37, 41-45 and 47 under 35 U.S.C. § 102(b) has been overcome and should be withdrawn.

Applicants arguments have been considered, but have not been found persuasive because the rejection is now not drawn to BCR-ABL being the compound encompassed by the claims, rather BCR is the compound encompassed by the claims for dyslocalization of BCR-Abl for the reasons set forth above.

9. Claims 37-39, 41-45, 47, 48, 49 and 77 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 01/73433 A2 (Minucci et al. October 4, 2001, previously cited) as evidenced by Nussey and Whitehead (Endocrinology: An Integrated Approach Box 3.9, 2001).

It is noted that given the indefinite nature of claims 42 and 43, given their broadest reasonable interpretation, claims 42 and 43 are drawn to the first binding domain having any binding affinity to for the tumor specific molecule.

WO 01/73433 teaches a fusion protein comprising the coiled coil (CC) region of the transcription factor PML, which mediates the oligomerization of PMR-RAR, fused to the full length p53 tumor suppressor protein. See page 12 and 61. WO 01/73433 teaches that CC-p53 is entirely localized in the cytoplasm, which would disrupt the nuclear localization of PML-RARalpha. See p.53. WO 01/73433 teaches that the p53-CC protein binds to p53 through the

p53 tetramerization domain and PML CC domain and prevents p53 from entering the nucleus; see pages 61-63 and Fig. 11. Thus the p53-CC protein is a protein comprising a binding domain for PML-RAR alpha, the PML CC domain, a second binding domain to effect dyslocalization, the tetramerization domain, and a DNA binding domain.

Additionally, WO 01/73433 teaches a fusion protein of the coiled coil domain of PML fused to an amino terminal region for targeting to the nuclear compartment (RBCC) and GFP. WO 01/73433 teaches that RBCC associated with PML-RAR-α, reduced PML-RAR oligomerization, and had an anti-leukemic effect on U937 cells expressing PML-RAR-α by increasing differentiation. See p. 1, 59, and 60 and Fig. 10. WO 01/73433 also teaches a fusion protein of the coiled coil of PML with the entire sequence of the human thyroid nuclear receptor CC-TR, which enhances transcription. See p. 59. Given that the thyroid receptor has a DNA binding domain for the thyroid response element and the coil coiled domain of PML mediates oligomerization, CC-TR would comprise a first binding domain for PML-RAR-α (coiled coil domain) and second binding domain for dislocation (the DNA binding domain for the thyroid response element). See p. 12, 59, Fig. 8 and Nussey and Whitehead (Endocrinology: An Integrated Approach Box 3.9, 2001).

Although the reference does not specifically state that RBCC and CC-TR delocalize PML-RAR-α to a site not that it is not normally present in tumor cells, inhibit the growth or induce apoptosis of a tumor cell expressing said tumor specific molecules, given that RBCC and CC-TR comprise the claimed domains and RBCC reduced PML-RARα oligomerization, the claimed product appears to be the same as the prior art product, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence

needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed method is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977).

Applicants ague that with regard to claims 37, 41-44 and 47, the Examiner stated that "the p53-CC protein is a protein comprising a binding domain for a tumor specific molecule, the tetramerization domain, a second binding domain to effect dyslocalization, the PML CC domain, and a DNA binding domain." Applicants respectfully disagree with the Examiner's rejection.

As discussed above, disruption of the HMW complex described in Minucci did not result in any specific dyslocalization or specific detrimental cellular effects. Therefore, the Examiner's characterization of Minucci is inaccurate, as Minucci relates only to the non-specific disruption of a HMW protein complex and does not disclose dyslocalization as defined in the present specification. Minucci also does not disclose the directed dyslocalization of a tumor-specific molecule that results in tumor cell death. Therefore, as Minucci does not expressly disclose every element of the present claims either alone or as evidenced by Prokocimer, Applicants respectfully submit that the Examiner's rejection of claims 37, 41-44 and 47 has been overcome and should be withdrawn

Applicants arguments have been considered, but have not been found persuasive because the PML-CC domains interacts with PMR-RARalpha and given that CC-p53 is entirely localized in the cytoplasm (see p. 53), this would disrupt the nuclear localization of PML-

RARalpha. Additionally, WO 01/73433 teaches other proteins encompassed by the claims as set forth above.

10. Claims 37-39, 41-49 and 77 are rejected under 35 U.S.C. 102(b) as being anticipated by Melnick et al. (Blood Dec. 2000, 96: 3939-3947).

It is noted that given the indefinite nature of claims 42 and 43, given their broadest reasonable interpretation, claims 42 and 43 are drawn to the first binding domain having any binding affinity to for the tumor specific molecule.

Melnick et al. teach purified AML1/ETO and PLZF-RARα. See Abstract and Fig. 1 and 3. Melnick et al. teach that AML1/ETO retains the domain for interaction with PLZF and interacts with PLZF. See p. 3941 and Fig. 1 and 2. Melnick et al. teach that AML1/ETO antagonizes PLZF transcriptional repression. See p. 3941-3942 and Fig. 3 and 4. Melnick et al. teach that AML-1/ETO disrupts the nuclear matrix compartmentalization of PLZF. See p. 3944 and Fig. 7. Melnick et al. teaches that PLZF-RARα interacts with ETO through the PLZF domain of PLZF-RARα and activates transcription of the retinoic acid response element.

Given that AML1/ETO can interact with PLZF through the ETO domain and given that AML1/ETO disrupts localization of PLZF, AML1/ETO would be a purified compound comprising a first binding domain, ETO, for PLZF-RARα and a second binding, AML1, to effect dyslocalization of PLZF-RARα. Similarly, given that PLZF-RARα has a first binding domain for AML1/ETO and a second binding domain, the DNA binding domain for binding the retinoic acid response, PLZF-RARα would be a purified compound comprising a first binding domain, PLZF, for AML1/ETO and a second binding, RARα, to effect dyslocalization of AML1/ETO.

Although the reference does not specifically state that AML1/ETO and PLZF-RARα delocalize each other to a site not that they are not normally present in tumor cells, inhibit the growth or induce apoptosis of a tumor cell expressing said tumor specific molecules, given that proteins comprise the claimed domains, the claimed product appears to be the same as the prior art product, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed method is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977).

11. Claims 37-39, 41-49, 51 and 77 are rejected under 35 U.S.C. 102(b) as being anticipated by Mao et al. (Blood Dec. 2000, 96: 3939-3947).

Mao et al. teach isolated MEF (myeloid ELF-1 like factor) that binds with AML1-ETO through its ETS-interacting subdomain (EID) and fusions proteins of MEF. See Abstract and Fig. 1-5. Mao et al. teach that MEF activates the IL-3 promoter through its DNA binding domain. See p. 3636-1st col., p.3639-2nd col. Fig. 7-9.

Given that MEF has a first binding domain, EID, for AML1/ETO and a second binding domain, the DNA binding domain for binding the IL-3 promoter, MEF would be a purified compound comprising a first binding domain, EID, for AML1/ETO and a second binding, the DNA binding domain to effect dyslocalization of AML1/ETO.

Although the reference does not specifically state that MEF delocalizes AML1-ETO to a site not that it is not normally present in tumor cells or inhibit the growth or induce apoptosis of a

tumor cell expressing said tumor specific molecules, given that proteins comprise the claimed domains, the claimed product appears to be the same as the prior art product, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed method is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977).

12. All other objections and rejections recited in Office Action of April 16, 2009 are withdrawn.

13. No claims allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter J. Reddig whose telephone number is (571) 272-9031. The examiner can normally be reached on M-F 8:30 a.m.-5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Peter J Reddig/
Primary Examiner, Art Unit 1642